patients that doesn't get antibiotics and they are compared to Deflux plus antibiotics? I mean, ethically, I can't see this being set up. And if we have an experiment where everyone gets antibiotics all of the time, I think the end required in order to have urinary tract infections would be quite large. I see practical problems in doing that experiment.

One question I have -- and, again, I'm not a physician who does it -- the material is said to be pseudoplastic, which can mean a lot of different things to different people in the physical sciences, and that it took 3 minutes to empty the syringe. Is there a problem of you have to push, push and then it all comes at once? The doctor is shaking his head. I think I can ask for a response, or not?

DR. ANTHONY KALLOO: Yes, you can ask for clarification. Just restate your name, please.

DR. AGERUP: I'm Bengt Agerup, from Q-Med, and behind the construction. Pseudoplastic will mean that -- no, it's not starting through force, it's just that by putting the product under the flow -- in the flow situation, the viscosity drops dramatically and then retains its viscosity when it stops again, so that in the tissue it has high viscosity, in the needle it has low viscosity. It simplifies the

procedure.

DR. BANIK: A few comments about submucosal and mucosal injection. As we heard today, there is the possibility of this material not actually halting in the area necessarily intended to. There's been some reinterventions associated with that.

Now, that needs to be referenced with the many techniques that exist today throughout gastroenterology and urology where submucosal injection is regularly used and, therefore, I feel the training curve term of physicians from an industrial perspective can be moved up rather quickly, and there will be complications associated with it being misplaced, but the learning curve would be relatively short since it's similar to techniques that exist today.

In terms of the pressure maybe to help with the questions associated with the time of -- by the period of injection on the syringe and the material being passed through the syringe seems very reasonable. You could look at even how long it takes to deflate a balloon in a cardiac dilatation or vascular dilatation, there's nothing here that I think based upon from an industry perspective that I see a little bit worse, and I think the results of studies

sort of show that the other risks or complications from the other inventions are more a cause.

So, the only other comment I have is relative to demographics. I think because of the construction of the study, the demographics response is skewed. It's difficult for those studies from an industrial perspective to be developed widely, and the cost really goes up. And I think we have to be sensitive to the data and the benefit of that.

DR. NEWMAN: My concern with these three questions is (1) we're looking -- I think these populations are more homogeneous. It's not so much whether they're white or black, they're more homogeneous when you come to states.

The second things is since we're really looking at efficacy with the one study, the third, I would have liked to have seen more sites because invariably you see procedures being done by individuals and they can't be replicated once they are put out across the spectrum here in this country, and it would have been, I think, much stronger to have seen several different sites and several different clinicians doing it, and that worries me that that wasn't done, or that it was offered and -- I don't understand why they didn't pick up the ball.

DR. DiLORETO: Again, echoing the previous comments, (1) at least from -- if there was a U.S. study, I think it would be difficult ethically to not have both groups of patients treated in an untreated group, not on antibiotics. I mean, I don't think anywhere in the U.S. would you find a group that would have known reflux not antibiotic treated. It just wouldn't happen.

So to build the study to do that, I don't think really would be an issue. It would be an issue of Deflux plus antibiotics versus just antibiotics alone. There's too much at risk to have these kids get recurrent infections and damage to the renal units that I personally, ethically, would not do that.

The demographics -- honestly, I don't think, as you've said, we know the stats of the populations that get reflux and, granted, that it was limited here, from the standpoint of other patients, but in reality I think probably is the least of the issues. Demographics is the least of the issues.

Multicenter versus single center I think is a huge issue. Single blinded versus unblinded reading is an issue. But I personally think the main issue is we're literally talking about 31 patients -- 39 in the treated group, 8 got selected out because of

the failures. We're talking about 31 patients only, and I've been doing this ten years. I've never seen a study where we have sat and made a decision based on 31 patients -- even if it's statistically significant -- 31 patients. The incidence of this disease is enormous. In our practice, we probably do 60 reimplants in a year in one practice. And we probably have 500 kids being followed with medical therapy. And so for me to sit and decide based on 31 patients, it's an overall issue, not the particulars that we're talking about.

DR. GORMAN: In terms of the specific question, I think we have about 210 patients for safety data over 2 institutions, and in terms of the short-term safety of the agent and the short-term tissue reaction to the agent, I think maybe there's enough data for safety short-term for both the procedure and the agent.

For efficacy, I would like to echo the comments of 41 patients, single institution, with a single investigator performing all the procedures, I think that is not generalizable to general practice of urology or to the general population of the United States.

DR. ANTHONY KALLOO: Dr. Kalloo, will you

summarize the Panel comments?

DR. NAIDA KALLOO: I think that, as I've mentioned, the demographics really is not the major issue. No, it did not reflect a wide range of demographics, but the demographics were probably adequate.

I think the big factor with compliance and antibiotics and having an adequate alternative is important, and I think that everybody sort of echoed that, but the alternative needs to be based on adequate numbers, and I think that from a short-term safety perspective the numbers are low, but people were not as concerned about the safety of things as they were about the efficacy, and the question is, is the data sufficient to judge this for efficacy, and I think that that was -- what I'm hearing from everybody is, there's a question -- that the data is just not significant to document the effectiveness.

The other thing is, again, the lack of long-term data. And the question about the differences among physicians on device usage, on the one hand, no, it wasn't adequately assessed in the study but, on the other hand, for those people who are accustomed to endoscopic procedures, the learning curve should be relatively short, and so that may not

be as big an issue.

And so, overall, I think that the adequate number of patients to assess efficacy is the big issue, was there an adequate number.

DR. ANTHONY KALLOO: Okay. Question 3, or Panel Charge 3.

3. The effectiveness of Deflux Injectable Gel is primarily based upon the comparison of reflux grades, per the International Classification System, among patients randomized between Deflux and antibiotic prophylaxis 12 months after initial treatment, Study 3. Although this grading system is the international standard for rating VUR severity, it is subjective in nature. In Study 3, the post-treatment grading of reflux was not performed by a blinded evaluator. Does the Panel believe that this potential for investigator bias significantly impacts the conclusions of Study 3 regarding device effectiveness?

Starting with Dr. Kalloo, we will go around the table for comments.

DR. NAIDA KALLOO: I think it was

mentioned that the evaluator was blinded -- I'd like some clarification, if I could get that. The evaluator, the radiologist that evaluated the films was blinded to the treatment type, is that true?

DR. CAPOZZA: Yes, you are right. Nicola Capozza from Rome. The evaluation was made by the radiologist, and they were blinded.

DR. NAIDA KALLOO: And they were blinded to the treatment.

DR. ANTHONY KALLOO: This was in Study 3?

DR. CAPOZZA: In Study 3. But it is also in Study 1 and 2. The evaluation was made by the radiologist.

DR. NAIDA KALLOO: And the radiologist did not know the treatment?

DR. CAPOZZA: They can, if they want. They can either look up the ultrasound and they can see the implant, for instance. But they don't know if that patient is part of the study or maybe is another patient treated out of the protocol, out of the study, maybe three or four years ago, or maybe with other substance, other materials. They don't know anything about our study.

DR. NAIDA KALLOO: And this was not one radiologist?

DR. CAPOZZA: Not one radiologist. Who is in charge that day of the system.

DR. NAIDA KALLOO: So there may have been variation just in their subjective evaluation.

DR. CAPOZZA: Yes. It could be, but as I told you before, the possibilities just between grade 0 and I and other -- any other grade of reflux -- that means II, III and IV. Now, II, III and IV is failure. We don't need to be so specific in grading reflux. We just want to know if they don't have reflux or they have just grade I, and that means just a little piece of ureter, or they have reflux, any grade of reflux.

DR. ANTHONY KALLOO: Thank you.

DR. NAIDA KALLOO: So I think in addressing this specific question, the evaluator may have been blinded, but it may not have been the same evaluator consistently per patient but, again, it's an issue of was there reflux or wasn't there, and I don't know that that's going to be -- it was either there or not, and I don't know that being blinded -- or I don't know that having the same radiologist read the study consistently through the study makes a difference in that case, it's a matter of whether it's there or not, but they also based their results on positive response versus a complete response. And if I'm not mistaken,

they've combined their results in some of their final results.

DR. DONATUCCI: I've already stated my previous concerns about the effectiveness data, but those concerns are not based on a concern about bias in this instance. I don't think bias here exists or has impacted the outcome.

DR. KAEFER: I agree. If one takes 0 as success and anything above 0 as not being success, I don't think bias plays a role in this. I do again believe that grade I is success.

DR. STEINBACH: I agree with Dr. Kaefer.

DR. BANIK: I agree also.

DR. NEWMAN: I agree with this one.

DR. DiLORETO: Can you see any of this on radiographic x-rays, any of the material? Does it show up in any form? I understand on ultrasound you can see it, but does anything show up different on plain radiograph?

DR. ANTHONY KALLOO: The question is, is the material seen radiographically by x-rays?

DR. DiLORETO: Goran Lackgren, Uppsala, Sweden. No, you cannot see it on x-rays.

DR. DiLORETO: Thank you. Again, I don't think there's any bias. I'll go back to what I had

said before, and Dr. Kaefer just re-re-echoed. Zero is success, I is not, and that obviously played into some of the statistical numbers that we're looking at that, again, are my issue of 39 or 31 patients. If there's not enough -- the blinding/nonblinding is not the issue.

DR. GORMAN: I don't think there's much concern about bias especially in the Swedish study where there are multiple hospitals and multiple radiologists. The systemic bias is hard to imagine. If the interpretation of the films remains a concern for other members inside of the FDA, the establishment of a radiology review committee for some subset film should be easy to -- easy for me to suggest -- probably very difficult to arrange where the films could be masked both for their order of read as well as the treatment status.

DR. KAEFER: If I can say one more thing, I think the concern for me is more pretreatment bias, and I would have a panel review them pretreatment because I think it could really affect the data if we call a III a IV or a IV a III. Post-treatment, I don't think the bias is a concern.

DR. GORMAN: I think if you are going to truly mask the films, you can mask them any way you

wish so that they can be read in any order -- pre, post, during --

DR. DiLORETO: But, again, that gets back into the covariables and how you want to stratify the data, whether it's the grade or in -- what I would be interested in is obviously age, which didn't come up in any of this data, other than just the average age, because as we all know there are times in the history of reflux where you would be more aggressive with lower degrees of reflux, given patients' ages, versus a high-high degree of reflux in patients that are younger, and stratification of that data would be an issue. And you're right, the pretreatment analysis again may make a difference, however, if there is reflux and you are entering them into the study, then the issue is how is the pretreatment compared to the post-treatment or the followup. But that gets back to just, again, blinding somebody just to look at all films, and in that particular case, probably a single interpreter would be the better person to be looking at that.

DR. ANTHONY KALLOO: I guess if the sponsor has data on success by age and also success in terms of going to stage 0, there will be a point that you can bring that up when I ask for your comments.

Panel Charge No. 4.

4. Given the rates of improvement in reflux grade and the rates of adverse events observed during the clinical studies and reported in the PMA, does the Panel believe that Deflux Injectable Gel has a favorable risk/benefit profile?

Starting with Dr. Kalloo, we'll go around the table for comments.

DR. NAIDA KALLOO: In a statement, I think there is favorable risk/benefit ratio, the question is the true efficacy.

DR. DONATUCCI: I agree. I think it's been documented that there is very little risk.

DR. KAEFER: And there's potential benefit. And one thing, if I can bring it up, I'd love for someone to address later is, very far back in all this how they looked at this issue of migration -- and I'm sorry I didn't bring it up earlier -- but that appears to be the big thing that really hit Teflon and the rest, at least as a clinician, that we would even touch the stuff if it migrated somewhere else. And I'm not really sure why the specific animal studies were done the way they were, but if it could be

explained to me -- there's some dog experiments in which after two years they look at H&E staining to look if there's any scarring or any reaction anywhere.

And then, following that -- and I would assume that chronologically they followed -- there's a study looking at 28 days in 6 rabbits to see if radioactive iodine has gone anywhere. And I really want to know, how did they pick 28 days and 6 rabbits, and is that really conclusive enough to say that it's not migrating somewhere?

DR. ANTHONY KALLOO: Would the sponsor like to respond to this? You can respond later if you would like.

DR. STEINBACH: I think the only risk I've heard about from this device is that the parents would take the child off of antibiotic after treatment, against the advice of the physician, because they thought this was a cure. Because of that, it has so few risks that it has a positive risk/benefit profile.

DR. BANIK: I think this has a positive risk/benefit profile. I, too, share the concerns about where this material is really going, and have the same questions about why the choices were for the studies that were published, and how they relate to the actual effects that we've seen.

DR. NEWMAN: I think it has a very low risk/benefit profile. I don't think it's an issue. And I thought they kind of did discuss about migration, the fact that they had up to two years. So, my impression was there wasn't a migration issue. But the other thing that this brings up, there must be long-term data on patients, if they've done literally thousands of patients. I know the FDA just asked them up to the one year, but they must have other data, and that could be one of our suggestions, looking at that data and pulling that into -- because they must have years of data on this.

DR. DiLORETO: I don't believe there's any issue concerning risk/benefit, but I'll go back to the comments about what "n" is in this study, and the number of subjects and the longevity of the study. You're right, there probably is data, but that's not part of the submission. We don't base anything on anything other than what's in front of us. So, I think there's the potential for this to be, having sat through a couple other panel meetings on other products in years past, an excellent chance that this is going to do something that we don't have that will be beneficial to these patients but, again, I don't think that there's enough numbers.

DR. GORMAN: I'd like to amplify on that statement. The efficacy, or the benefit of this, if it holds up from the small numbers, would make it seem fairly efficacious. I think the risks to this point are we touched on the substance doesn't appear to be terribly risky, but the long-term efficacy and the potential for later undiagnosed or slowly diagnosed failure rates concerns me as a pediatrician, that if two years from the time of injection you start to reflux again, as the substance is either absorbed or the ureter grows in caliper, makes the long-term risks for this substance still unknown.

DR. DiLORETO: Can I just jump in here for a second because this is an important point. Given a cure, assuming 0 is a cure, and two or three years later patients have forgotten, if they even knew because they were too young, or parents had forgotten, and there is an issue of asymptomatic infections in kids, although it tends to decrease I think as they get older and have more ability to have more symptoms, but it can become somewhat of a moot point and ignored where then some -- you know, you don't have reflux, you've been treated, it's gone -- repeated infections that then could lead to renal damage is still an issue. And if I've been cured, then it's got to be

something else, and they don't -- they are not treated or worked up or followed appropriately.

DR. GORMAN: And I guess that's why I continued or I tried to make clear there was a discussion about antibiotics in conjunction with this particular device use, which I think is limiting the scope of the total continuum of care that might be provided for these patients -- antibiotics, frequent urine cultures or frequent urinalysis -- as you go forward to long-term monitoring of these patients.

DR. DONATUCCI: I just want to make one further comment about risk. When I considered risk and made my statement earlier, I wasn't thinking until Dr. Steinbach made a comment -- there's one additional risk which is not incumbent upon the material itself, and that is the fact that this -- many of the children who now would be treated with antibiotics would be subjected to a general anesthetic to place this device, and there is some increased risk in that population based upon the anesthetic use.

DR. KAEFER: If I could clarify my statement regarding the safety, I meant to make no statement regarding how safe it was, I want to know why these endpoints were chosen.

DR. ANTHONY KALLOO: Dr. Kalloo, would you

summarize the panel comments?

DR. NAIDA KALLOO: I think based on the data, there are unknown risks that we just don't have enough information about -- the risk of migration short-term appears to be low, but we don't know (a) enough about how -- there's a question of how this was determined and what the endpoint was, and the risk of migration long-term, there is also again, as has been reiterated many times, inadequate long-term data, so we don't really know what the long-term risk is.

We also have the risk of general anesthesia, which is low particularly in a healthy pediatric patient but, again, it's not 0, and again the issue that keeps coming up is, are there adequate numbers of patients to really discuss efficacy for the risk/benefit ratio. It does appear that overall it is a favorable risk/benefit ratio.

DR. ANTHONY KALLOO: Panel Charge No. 5.

5. Is postapproval study/surveillance needed to address any unresolved safety and effectiveness issues? If so, please specify the type of study needed.

Starting with Dr. Kalloo, we will go around the table for comments.

DR. NAIDA KALLOO: I think we've been making these statements all along, and I'll just reiterate the ones that I've been hearing consistently. (a) The long-term effectiveness; (b) should this be considered cure after one VCUG at 3 months, after one VCUG at 12 months? What do we do in the interim to prevent potential renal damage? Do we keep these patients on antibiotics? The other questions are -- I'm sorry, I lost my train of thought.

So, the migration, the long-term efficacy, the long-term side effects I think are the big questions, and what type of study -- what do we do after a year, do we continue to monitor them just with urine surveillance, and if the urine cultures are positive, at that point do we do a VCUG? If they were negative at a year? Or do we decide to do a VCUG as a standard protocol at 2 years to see if the durability has held up?

DR. ANTHONY KALLOO: So what would you suggest?

DR. NAIDA KALLOO: I would suggest that if we go with it as is, that I would continue to do surveillance. If there us a cure rate at 12 months, then I would stop -- I would continue antibiotics

until 12 months, and at that point if there appears to be a cure, then I would continue on with surveillance urine cultures and renal sonagrams just as I would after open reimplantation, and maybe get a VCUG at 2 years.

DR. DONATUCCI: I agree, I can't add anything to that.

DR. KAEFER: In addition to that, there are a number of patients I see who have asymptomatic bacteria, and I don't think it would be that involved to simply screen for asymptomatic bacteria in these patients after 12 months with urine dipsticks, and do it at frequent intervals. We have damage from vesicoureteral reflux in the face of infection. If we can show -- or the people who are proposing this can show that for 2 or 3 years that you're free of infection, then that would be very helpful.

DR. STEINBACH: One of the things the FDA uses on most devices is they have -- I'm not sure what it's called now, a MOD -- where there's this device reporting system, so if someone finds a defective heart valve, they recognize it as such, and they call up the FDA and tell them about it.

Many physicians would not recognize this as a device, certainly, if they weren't the ones that

put it in, so this aspect of the FDA reporting system may not apply.

On the other hand, we have to balance this against -- if we keep it off the market for 10 years in order to get a 10-year study, that puts a portion of the public at potential risk that they wouldn't otherwise be exposed to.

I think the end result issue is, is it good for 5 years or so? But I'm not sure that that can be handled by -- under the provisions of least burdensome evidence we can ask the company to do this.

DR. ANTHONY KALLOO: Again, remember the question is, do you think that there is postmarketing study or surveillance needed and, if you think so, what are the things that the study should -- what should we be looking for in the study? That's the specific question.

DR. BANIK: I think post-market surveillance is desirable, and we don't get the usual kind of surveillance we get with other devices because it's not recognized as such. So we would have to rely on the physician who uses it to keep track of his patients and report failures. This probably would come up with labeling.

DR. SEGERSON: I just wanted to clarify

that even drugs has reporting of adverse events. I think we would find out if a report were submitted, but I also want to point out that postmarket surveillance is something that happens regardless of what we might impose on this manufacturer. All we're looking for here is a recommendation as to whether you want a prospective-structured study that the manufacturer would have to conduct for some period of time and yield data that you think you need.

DR. ANTHONY KALLOO: In fact, with that comment, I'll start again and ask people for their comments. So the question is, is a post approval study needed? Yes. And, if so, what structure should it be?

DR. NAIDA KALLOO: I would say a VCUG at 3 months, 12 months, and 2 years. I would continue antibiotics until the 12-month VCUG, and I would do surveillance urine cultures at 3-month intervals and with any symptoms or changes in urinary habits.

DR. DONATUCCI: Yes, a study is needed. It needs to be multicentered with multiple investigators. It needs to be of sufficient time to document the efficacy of the treatment over time. And obviously I think they would be collecting safety data, in addition. I'll defer to the pediatric

urologists in terms of the specific studies that they would want, and antibiotic coverage.

DR. SEGERSON: While you're commenting on the study, could I ask you also to maybe address the issue of the size of the study, how many patients?

DR. KAEFER: I'd say in the short time or the time I've had to think about it, I think your suggestions are very good, and I would go with those with the thoughts I've had so far. And I would defer to statisticians in terms of how the study should be. I don't know.

DR. STEINBACH: The statisticians say that if you have enough patients to show significance, then that's enough. But the clinician saying -- I just don't believe 30 -- and because based on variations, 30 is too likely to be a random sample -- or nonrandom sample.

DR. ANTHONY KALLOO: I don't think it's fair to ask for a number of patients in a study just off the bat. I think it requires statistician and software and data.

DR. NAIDA KALLOO: Shall we say more than 39?

DR. STEINBACH: Also, the other thing that's coming up for number of patients is that we

would like to be able to show that the grade IV cure rate is significant for patients older than 10 or something like that, so that when we start breaking down these variables like age and degree of severity, the number will go up, if we have to show that those subset groups is -- each subset group would be affected.

DR. BANIK: Maybe to break from the trend here a little bit, one of the difficulties I see is in sort of the information as presented to us were presented with these three studies. It seems to me that apparently in the background there may be some more favorable data that this manufacturer has that they haven't really been able to compile in a professional manner to be able to get it in front of this group for --

DR. ANTHONY KALLOO: Or maybe unfavorable.

DR. BANIK: Yes, either way -- to be able to make people think a little more about this and come up with better conclusions. So, one thing relative to maybe not necessarily a clinical study, but relative to maybe an animal study that I think would make me feel more comfortable with the data presented would be possibly a different look at the kind of data that we got on the longevity of this material and what happens

to it.

I think we've heard things from what they have given us in terms of -- that there is movement of this material that may not be accounted for, where you have to have a second intervention. The short-term duration of the animal studies that were presented, even though we did have -- they didn't present a two-year study -- it doesn't show us any degree of confidence in what's happening three years, four years, five years out.

So, I think in addition to looking at those things that the others have recommended, I think it would be good to look at some of the scientific data, maybe some half-life studies on the material, to try to provide some scientific data on what the real degradation rate of this material is, and its effects in tissue.

DR. NEWMAN: I'm a little confused because as I read this question, you guys sound like you're designing a new study for them to do as a postapproval surveillance, right? So the concept here is, if it's approved, then what is it we want them to do with this study, correct? What additional information we want on this study, No. 3, right?

DR. ANTHONY KALLOO: Or if you think

further studies are needed pending final approval.

DR. NEWMAN: Well, if you approve this, it will just be used, and then are you going to do more studies?

DR. BANIK: It's two different questions.

DR. NEWMAN: I know. I mean, it doesn't make sense. It doesn't kind of make sense to me. Again, I'm back to, if you take their study and it would get approved, I would like to have them present more data on the long-term, the different age groups, is there differences between whether the child was in this age group or whatever, what other information do they have on the studies that they presented here that could give us more data, the FDA more data, to be more conclusive about the usage of this product in this country.

DR. ANTHONY KALLOO: Could the FDA just clarify that question, what they are looking for in terms of an answer?

DR. SCHULTZ: Can I try?

DR. ANTHONY KALLOO: Yes.

DR. SCHULTZ: I think some of your confusion is well founded. I think the way the question is written, basically what we are saying is, if the device is approved based on the study that has

been done and the data that you've looked at, given that there could be some additional information that could be extracted from that data, from the studies that have already been done -- and you certainly may feel free to request that those additional analyses be performed -- if, after all that you say that the device could be approved and could go to market, then the question is, is a post-approval study/surveillance needed in addition to that?

Now, the design of that study could be something as simple, or your recommendation could be something as simple as look at the patients that you've already treated and see what kind of follow-up was done and make sure that those patients get followed up at 2 years, 3 years, 4 years, 5 years, and come back to us with reports that followed those patients with respect to whatever you want -- migration, persistence of urinary tract infections, and additional x-ray studies that could be done at 3 years, 5 years, whatever you want.

The other option is that a whole new study be designed, that you're saying that there aren't enough patients that, dah, dah, dah -- you know, we need another study, another cohort, whether it be there in Italy, in Sweden, in this country, wherever

it might be, to address any of these issues that have not been fully addressed in the premarket study.

So, I hope I haven't you confused you more, but basically you have a lot of different options. You know, you have options with respect to premarket data, and you have options with respect to postmarket data.

DR. ANTHONY KALLOO: Thank you. So this means we're on the right track thus far.

DR. NAIDA KALLOO: I wanted to ask a quick question. The end of the study was when? When did you complete your 12th month VCUGs on Study 3? When was that completed?

DR. CAPOZZA: Nicola Capozza. It was in September 1990.

DR. NAIDA KALLOO: So we are now at the 24-month --

DR. CAPOZZA: Yes.

DR. NAIDA KALLOO: Is it possible to gather up those patients and gain data at this point? Are you still following these patients?

DR. CAPOZZA: Yes, of course. It is possible.

DR. ANTHONY KALLOO: Thank you. Let's continue.

DR. DiLORETO: That was a very nice synopsis because the premise is "if", and I had a problem with that because there's a premise that's "if" first. "If" the answer is yes -- or, actually, if the answer is no -- I think the same question needs to be addressed, and the answer to the question ought to be followed for at least a couple -- two or three years -- followed with VCUGs at 3 and 12 and probably 2 years, followed with urine analyses, followed with -- you mentioned, Dr. Kalloo, but I think it got dropped a little bit -- ultrasounds from the standpoint of there appears to be an obstructive component that potentially can exist in this group, and whether that obstructive component potentially leads to other problems -- upper tract issues or infections -- not based on reflux, but just based on obstruction.

So, the answer is yes. Whether the first premise is yes or no, the overriding issue is there ought to be postmarketing surveillance, and I think the clinicians probably can get together and come up with some -- with FDA personnel -- come up with some legitimate, valid, safe way to monitor these kids, but they absolutely have to be followed.

DR. GORMAN: I think my urological

colleagues have taken care of the clinical followup of the individual patients, but from a public health perspective I'd like to suggest three potential studies for postmarketing surveillance: (1) In centers where Deflux or some other agents of that type are used, I would want to see anyone who was subsequently admitted to hospitals in that region with a diagnosis of pyelonephritis, what fraction of them had previous Deflux therapy. I would also like to know what percentage of people who had surgical reimplantation of their ureters had previous Deflux therapy. Then I would like to go to the National Cancer Institute and from their database of bladder cancer in children and young adults, look at all bladder cancers to see how many had previous Deflux therapy over the period of the next five to ten years.

DR. ANTHONY KALLOO: Dr. Kalloo, would you summarize the Panel comments?

DR. NAIDA KALLOO: I think that the main issues were if it is approved, do we need postmarket surveillance, and the answer was twofold: (a) if it is approved, we would need certainly more premarket information -- for example, more information about the patients who are in the study, or who were in the study at the 2-year mark, and do we need postmarket

surveillance, and the answer is, yes, we need postmarket surveillance. What would that be? And it was brought up that we could certainly continue antibiotics, get the VCUGs at 3 and 12 and maybe 24 months, continue to monitor them with ultrasounds and surveillance urine cultures at 3 month intervals. Whether this needs to be multicentered with multiple investigators would certainly address some of the other issues that have been brought up before.

The other question is, if it's not approved, what needs to be done with the information that we already have that would make it more approvable, and that goes back to, again, if more information about the patients that were in this study, and could we design a study here in the U.S. that would address some of the issues that we've already brought up. And, again, potential postmarket studies would be the incidence of urinary tract infections in patients after surgical reimplantation, the incidence of urinary tract infections after Deflux, and the incidence of bladder pathology in patients who have undergone Deflux.

DR. ANTHONY KALLOO: Panel Charge No. 6.

6. If approved, should physician training be required prior to use of Deflux

Injectable Gel? If so, please comment on the specific type of training needed.

Staring with Dr. Kalloo, we will go around the table for comments.

DR. NAIDA KALLOO: I think a video for most experienced urologists would be adequate.

DR. DONATUCCI: I don't think any mandatory training is necessary. I think voluntary education is, of course, important.

DR. KAEFER: I'm a Pediatric Urologist, and I'm with three other people where I work now and was with seven other people before I moved to this job. And as a Pediatric Urologist among those ten in the United States, I would say that I rarely saw anything injected through a cystoscope, and that's very different for an adult urologist or urologists who do both.

We have two who are actually investigators of recognized competence who injected this substance, probably injected Teflon and other things before that, and so at this point, I don't know. I think that it could be beneficial to me, and I'm only trying to think of how I can avoid injecting it in the wrong place, how I can make sure I put it in the right plain so I don't have to retreat patients. I think for me

personally, I think it might be very beneficial actually to take a course, and I don't know what animal model they used to train people to do it in Europe, but that may be helpful for me and others.

DR. ANTHONY KALLOO: So you recommend a hands-on training course.

DR. KAEFER: Again, from my personal viewpoint, I think that might be appropriate.

DR. DONATUCCI: I just would like to add, we've been down this road before with another injectable. I remember it quite vividly. It was not -- this was mandatory training with expense involved. It was not well received. And we're opening up a Pandora's Box if we require mandatory training.

I don't feel that the skills involved here -- yes, there's a learning curve, as there is with any surgical procedure, anything new that we do. But this is so unique that mandatory -- and with the force of the Government behind it -- is necessary.

DR. STEINBACH: I would be reluctant to require mandatory training.

DR. BANIK: I don't think mandatory training is required. I think there's other devices in other areas that are used through scopes that the FDA knows what their complaint rate is. There are

various manufacturers throughout the world who make devices for injection similar to this. Though it may not be something that the urologist is used to doing, I think it certainly would be quickly, from an industry perspective, adapted, and if some kind of video, as suggested earlier, or CD Rom, or something with sort of an explanation I think would be adequate.

DR. NEWMAN: I don't have anything to add.

DR. DiLORETO: I would agree with Dr. Kalloo that the type of technique -- and with Dr. Kaefer -- is intended to be more of a kind of adult urologic procedure injecting things, and the pediatric urologic community may not be all that well versed in doing that, but a simple video -- it's eye-hand -- and a simple video would suffice. And, again, with Dr. Donatucci, because I also happened to sit on one of those panels -- mandatory is not the way to go with this.

DR. ANTHONY KALLOO: Does it have to be mandatory?

DR. KAEFER: I didn't mean to imply mandatory, but if some mechanism would be available for someone to do something like that.

DR. DiLORETO: We have it within our ability to make it mandatory because I've been on

panels when we've done that. And, again, physicians trained in the use of this. Now, what that entails could be simply package -- could be videos, could be training dummies, or something -- but there are times when the Panel has dictated mandatory training for certain things -- lithotripters, other things. This just doesn't happen to be one of them, in my eye.

DR. ANTHONY KALLOO: Dr. Gorman.

DR. GORMAN: I guess I look at training a little differently, not being technologically enabled. The role for this particular intervention doesn't seem to be clearly defined in my own mind, and I guess I'm more concerned -- when you said about putting it in the right place, I wasn't concerned about where near the ureter it went, but which patient it went into. And I guess the candidates for this particular procedure would be the part of training that I would like to see emphasized, either through the labeling of this device as it gets out there, who is an appropriate candidate for this particular procedure, and under what circumstances, and I think that can be handled through labeling rather than through mandatory training. I would assume that my colleagues in the urological field would have the technological finesse to be able to learn to do this quickly, using whatever

mechanism they felt was most appropriate.

DR. DiLORETO: Can I jump in again, because this has come up at other Panel meetings, and this, I believe, would be addressed in a labeling issue. Urologic physicians trained in management of vesicoureteral reflux that have the wherewithal to know how to follow these kids, know how to treat them, know how to manage them, possibly not know how to do an operative procedure because there are adult urologists that potentially could be treating these kids if they were adept in the management of this and given the geographics of where -- there are not pediatric urologists everywhere in the country -- and, again, some of these things could be handled from whence they came, or they wouldn't need to go to the big meccas to get treated. But that particular individual would have to be adept in the management of vesicoureteral reflux, all of its aspects, probably short of reimplant surgery. I think that just carries forward a little bit what you were talking about.

DR. ANTHONY KALLOO: Dr. Kalloo, will you summarize the Panel comments?

DR. NAIDA KALLOO: I think that, by and large, the training should not be made mandatory, but it should be clear from the packaging that the

physician performing the procedure should be well versed in treating the entity of vesicoureteral reflux and that training should be made available in the form of a video or even hands-on training by the company representative in any way possible, but that mandatory training should not be necessary, but voluntary training should be available.

DR. ANTHONY KALLOO: Thank you. Panel Charge No. 7, the final charge.

7. Are the proposed Directions for Use accurate and comprehensive? If not, please recommend any revisions or additions.

Starting with Dr. Kalloo, we will go around the table for comments.

DR. NAIDA KALLOO: I think we've sort of addressed this in a roundabout way in that it's already been brought up that we need physicians who are well versed in the treatment of vesicoureteral reflux, and I don't recall seeing anything specifically that said "Directions for Use". Was there a --

(Simultaneous discussion.)

DR. ANTHONY KALLOO: Why don't we go ahead with Dr. Donatucci's comments.

DR. DONATUCCI: The material that I read here seems to be fairly comprehensive. I think video, which they've already prepared and showed us in part this morning, is helpful also. The labeling changes as recommended by Dr. DiLoreto I think would be helpful.

DR. KAEFER: No further comment.

DR. STEINBACH: The patients with the Hutched diverticulum were excluded in the studies, but it's not listed as a contraindication. Again, as an engineer, I get to ask what is a Hutched diverticulum, and should this be listed as a contraindication?

DR. KAEFER: A Hutched diverticulum is a weakness in the bladder next to the ureter. Hutch was the gentleman who first described it, and it potentially can affect the backing of the ureter. It's typically superior and lateral to where the ureter is, which is, based on everything I've seen here, just in the opposite direction of where you're going to be bulking up the ureter.

DR. STEINBACH: So you would not consider it a contraindication?

DR. KAEFER: I guess I can say that I probably would consider it a contraindication. And I overlooked that, I'm sorry.

DR. STEINBACH: In the brochure handed out to the patients, they said the other material would be either Teflon or silicone, and then they go into a description of risks of silicone that haven't been verified. And I think since there is a risk that a quarter of these patients will need further care, some of which might need a silicone tube, that this ought to be out of the instructions to the patients. Just leave it as "other alternatives are Teflon and silicone", and don't give weight or authority to a possible cancer risk because that hasn't been proved scientifically.

DR. ANTHONY KALLOO: Dr. Kaefer, you had mentioned earlier about dysfunctional bladders, is that --

DR. KAEFER: As part of this overall education of treating this that you had mentioned, had mentioned a number of times, and I did mention it earlier and I asked Dr. Capozza. Treating dysfunctional voiding prior to using this device I think is very appropriate -- in fact, it should be mandatory because you could treat it and cure it, and does.

DR. SCHULTZ: Could I just provide one clarification since it's come my way. I just want to

make sure -- and it sounds like you're already addressing this -- but when we say there "Directions for Use", we're talking about the entire label, not just the directions how to inject, and this was something that you brought up earlier about patient selection criteria. Is the indication statement as proposed appropriate? Are the contraindications appropriate? Are the warnings/precautions appropriate? That is all on the table, fair game. We'd love to hear your comments on all that. Thank you.

DR. BANIK: Two things. In the document that I have -- I'm not sure, I think this is a patient brochure -- it reads that the biodegradable material is in place for three to four years or more. And the question I think I asked earlier, that wasn't evidenced, and unless I misunderstood the gentlemen, I don't think they had data to back that up. So, my recommendation is that that be struck from the label copy.

The second --

DR. ANTHONY KALLOO: Do you recommend replacing it for "an unknown length of time", or --

DR. BANIK: They have one-year human follow-up data that was presented to us. Unless we

see more concrete data, I recommend we use the data that was presented to the FDA. That's viable if they want to make that claim, but certainly it has to be substantiated, in my opinion.

The other area that I have some concern about is the last sentence. It says "the clinical cure rate has exceeded 80 percent in preliminary long-term 3-5 year followup", which would lead practitioners to believe that obviously that there's data out there on 3-5 year followup, which may support the claim that I've just asked them to strike, and this is data on file at the company. I don't believe that was shared with us. If that data has not been shared with us, I question whether that statement should be in there, or that we should ask for that data to be able to substantiate that claim in the label copy.

DR. NEWMAN: Again, it's hard for me to comment on this because I'd like to know the age group. I think there could be more information on here depending on the age. There's a big difference between a 2-year-old and an 8-year-old, and there should be more on patient counseling then. You know, how may repeats? Is it in a certain group? I don't know. You know, you have nice tables here, but you

don't give ages. I think there's a difference in girls and boys. I mean, you know, if I've got to keep doing urine cultures on my girl that I've got to put a pouch on her as opposed to guys that stick out, so it's different. It's different to get this stuff as a parent, and you don't have information here, and I think it's because it's a problem with the fact that you're not giving us enough data on it, but I would like you to put more in here so you give the physician more information so he can say to a parent of a 3-year-old, "This is what's going on", a parent of a 9-year-old -- this is the way we make some sense. You know, is the 9-year-old going to have to be reinjected because our data shows "X" whereas another child maybe no. I don't know, maybe because there's not that information here, I have a hard time looking at this and coming up with some good suggestions.

DR. DiLORETO: Again, the premise is "if". Getting past the "if" premise, this obviously was some kind of a handout I think that was probably used overseas, not for the U.S. There's no injectable material that's available here in the U.S. and, hence, you cannot have any comparison against any other treatment modality other than what we're doing right now.

This can be done in committee with the FDA, with some of the panelists, in an after-approval methodology, because I've seen it happen before, but there has to be specific inclusion and exclusion criteria built into this. Hutch is one. The nonfunctions shouldn't be put in here. The duplicated ureters, there's no data on duplicated ureters. There's actually not a lot of information on the dysfunctional voiding. And there's a whole multitude of inclusion/exclusion criteria that need to be built into a label if it's approved.

There ought to be -- the study doesn't give us the numbers -- there ought to be something in there based on ages, gradation of reflux, ages of the patients, chances of spontaneous remission versus -- other issues -- again, the numbers don't support that, there are enough numbers to look at it from that standpoint -- but if you were to approve the product and if you were to have a label, there would have to be a significant -- this one goes away -- I mean, other than the nice pictures, which I think are good -- there's nothing in there that should exist, from my standpoint, that we would want. It would have to be start afresh.

DR. GORMAN: I've always believed in

evolution, not revolution, so I'll try to edit this just a tad. If the data we were presented today is used to approve, the labeling here says "For treatment of vesicoureteral reflux in children" -- I think that's untrue. It's for grades II-IV. There's no data presented on grade V.

Second, there is a section on patient counseling information, some of which I would wish to be put up into the "Warning". As a physician, when I try a new agent, the only thing I read is the Warning or the Contraindications because I already know why I want to use it. So I would put in there in the Warning the phrase that goes, "The patient should be advised" -- or it should just say, "Deflux may not give a permanent therapeutic result and additional treatment sessions may be required to maintain the effective treatment". And then I would completely rewrite the Patient Information section to give them the complete range of therapeutic -- perhaps not the complete range, but a wider range of therapeutic options that they can have from antibiotic therapy, surgical reimplantation, or natural evolution, depending on whether you come from California or not, and nobody takes antibiotics anyway.

DR. ANTHONY KALLOO: Thank you. Dr.

Kalloo, will you summarize the Panel comments?

DR. NAIDA KALLOO: Before I summarize, I just want to make a comment. I've read through this whole thing, and when it says "Directions for Use", that didn't correlate for me with device labeling. There is no "Directions for Use" here.

But in the device labeling, I think that overall there has to be major overhaul in both the device labeling and the patient handout. And I think that (a) this doesn't reflect -- like has been mentioned, it does not reflect the data that we have been given, this greater than 80 percent cure rate over 3-5 years is nowhere in the data that we have. And if we had access to that information, as has been mentioned, I think that would help us, but I think a major overhaul, and I think that that would have to include and exclude specific things, such as contraindications to use, what patients based on age, gender, grade of reflux. I think that it is important for both the physician and the family to be informed about comparing this treatment with open surgical treatment and with the natural history of reflux and spontaneous resolution with antibiotics.

The other thing is -- I think overall that's what everybody's been saying, that we need to

specifically include and exclude things, and that these are the major overhauls if this is to be approved.

DR. ANTHONY KALLOO: Thank you.

Before we take a vote, does anyone from the public wish to address the Panel? Please raise your hand and you may have an opportunity to speak.

(No response.)

Does the FDA have any comments?

(No response.)

Does the sponsor have any comments?

(No response.)

DR. DiLORETO: Goren Lackgren, Sweden. Just a few comments and some responses to what you said. First, about migration. It is generally considered migration occurs by direct injection into the vessel, and that occurs immediately. So in the rabbit setup, it was sufficient, they said, to look at that after 28 days because late migration do not actually occur even in Teflon and silicone, it happens immediately. So I think that's sufficient.

And I just would like to say how we are looking upon that now in Sweden. We have been treating that since 7 years, and we are following our patients like we follow the normal reflux patients,

which means that we give them prophylaxis until the reflux is gone. So that means after 3 months or 12 months or whenever.

Furthermore, we have very few late recurrencies, late infections, because we don't repeatedly are doing VCUG because it's a very painful investigation. One should be aware of that. So, I mean, a study with performing a lot of VCUG afterwards is of little value if they are without infection. That is clinical signs. And, to me, that is the most important thing. And, of course, if there would be a lot of clinical infections, then you should do the VCUG.

So the important thing is to follow these patients, which we are doing, and we have very few late recurrencies. That is just a comment.

DR. CAPOZZA: Nicola Capozzo, Rome. We follow our patients in a similar way, and what we do now is a scintigraphy with MAG-3 scintigraphy that allows to have a cystogram at the end of the examination. You don't need to put a catheter and the ablution is very low. So maybe the second cystogram two years later could be this kind of examination.

DR. NAIDA KALLOO: You're doing that with MAG-3 through an intravenous line?

DR. CAPOZZA: Yes. And at the end of the examination, you can ask the patient to drink in order to fill the bladder, and when he wants to urinate you can put him on the screen and see if there are reflux.

DR. KAEFER: Some of the difficulty with that, though, is that if there's any left in the ureters, you might miss the low --

DR. CAPOZZA: No, because MAG-3 has the property to leave the kidneys very rapidly, very quickly.

DR. KAEFER: So it assumes the patients have cleared it.

DR. CAPOZZA: Yes. And alternative could be a cystosonography by ultrasound, but you can avoid the radiation but you can't avoid the catheter. But it's an option in the long-term followup.

DR. DiLORETO: You're also assuming the ureters are draining normally, correct?

DR. CAPOZZA: Yes.

DR. NAIDA KALLOO: If there's any impairment in drainage, the MAG-3 is still going to be there after voiding, not -- I mean, there could potentially be a false-positive based on an anatomic issue or an obstructive issue. I understand it's a nonionizing test and there's benefits for it, but in

reality it's not the definitive test for VUR.

DR. CAPOZZA: Yes, but there is the radioisotope in the bladder. Wherever it comes, from the one side or the other side, you can still have a cystogram, the radioisotope cystogram can be direct or indirect. This is indirect cystography.

DR. KAEFER: I don't have the perfect test for looking other than putting --

DR. CAPOZZA: I mean, it's a proposal for a long-term followup.

DR. KAEFER: The ultrasound approach, I've reviewed a number of papers for the various journals, and that does have a fair amount of error involved in it as well, so it's not perfect. It is another possibility.

DR. CAPOZZA: It's no my favorite. And I want to make a short comment on the antibiotic patients, the one who didn't give the diary. The diary was complementary, it was not the main part of the study. Also, we have no reason to believe that these patients didn't comply with the prophylaxis, they just lost it and they forgot to give it to us.

DR. NAIDA KALLOO: In the study, these patients were treated for one month with antibiotics after implantation of the Deflux. They were not

treated until success was confirmed, is that correct?

DR. CAPOZZA: Yes, in Study No. 3. In Study No. 2, they continued until cystogram at 3 months.

DR. NAIDA KALLOO: And then if it was negative, if there was no reflux at 3 months, the antibiotics were stopped.

DR. CAPOZZA: They were stopped.

DR. NAIDA KALLOO: And then the patients, the 7 UTIs in that group were in patients who subsequently failed between the 3 and 12 month VCUGs.

DR. CAPOZZA: Yes, that's true.

DR. DiLORETO: Off the antibiotics.

DR. NAIDA KALLOO: Once they stopped the antibiotics after the 3-month VCUG, then all the UTIs were between 3 and 12 --

DR. CAPOZZA: There is a problem about the study design because we have a lot of information from the Deflux group, and few information from the antibiotic because the first group was followed up very closely, and the other group we don't know anything about this 12 months because we saw the patients at point 0 and 12 months later.

DR. NAIDA KALLOO: Were they asked --

DR. CAPOZZA: This would be a possible

explanation, the lack of this asymptomatic bacterurial infections in the second group.

DR. NAIDA KALLOO: Were they asked if they had urinary tract infections?

DR. CAPOZZA: Yes, of course, but it depended on the frequency they performed the urinalysis.

DR. ANTHONY KALLOO: Thank you. Next, I'm going to ask Dr. Kalloo to summarize all the Panel comments from all the Panel discussion points that were raised.

DR. SCHULTZ: Dr. Kalloo, could I just ask one more time, did the sponsor have any other comments, any representative of the sponsor have any additional comments that they'd like to make before the Panel makes their deliberations?

DR. NEWMAN: You said you ended Study No. 3 like a year ago. When did you start it? When was the span of the study?

DR. CAPOZZA: The study started in September '98 and ended September '99 -- October '98 to September '99.

DR. NAIDA KALLOO: Study 1?

DR. CAPOZZA: Study 3.

DR. NAIDA KALLOO: What about Study 1,

when was that completed?

DR. CAPOZZA: Generally, '95 -- oh, Study 1 -- sorry.

DR. DiLORETO: Goran Lackgren, Sweden. Study 1 started '93 and was completed '94.

DR. NAIDA KALLOO: Do you have any long-term data on those patients?

DR. LACKGREN: We have followup our patients, so all of the patients are followed. So we have treated 500 patients.

DR. SCHULTZ: Could I just clarify? The question is, is there data. We understand that you followed the patients. The question is, is there data available to supply either to the Agency and/or to the Panel.?

DR. LACKGREN: Not in a study fashion, but we have followup data.

DR. CAPOZZA: We have data about Study No. 3 available even after the end of the study.

DR. NAIDA KALLOO: And how about Study 2, when was that completed?

DR. CAPOZZA: We don't have many data because it was in old fashioned way, the study, and also patients did not sign specific consent for inspection of data. Patients in Study 3, they signed

consent even for an inspection from other people, other countries produced them because we asked them for this consent. In Study No. 2, it was asked but they didn't sign the specific form.

DR. NAIDA KALLOO: You've heard us on numerous occasions suggest that we need more long-term information. Is it possible to get that long-term information based on the three studies that you've done?

DR. CAPOZZA: No problem for Study 3. For Study 2, we can ask the patients to give their consent to data, whatever we want.

DR. LACKGREN: Yes, it's possible to get data for long-term followup in all our patients.

DR. NAIDA KALLOO: So if that something that we decide is necessary, that would be easy to do -- well, not easy -- but it would be available.

DR. ANTHONY KALLOO: Thank you. Can we show each question as Dr. Kalloo summarizes again the comments from the Panel?

DR. NAIDA KALLOO: Charges to the Panel.

1. Based on the patient population enrolled in the clinical investigation of Deflux Injectable Gel and reported in the PMA, should the intended use statement

specifically limit the use of Deflux Injectable Gel to patients with particular grades of vesicoureteral (VUR); for example, grades II-IV reflux as enrolled in the clinical studies?

In summary, I think that we discussed grade IV, and I think we needed more specific information about grade IV, but we should not necessarily limit it, we just wanted some more information.

2. The primary study, Study 3, was conducted at a single center -- Rome, Italy. Typically, pivotal clinical trials are performed at multiple institutions to evaluate the outcome of device use on a divers patient population in the hands of a variety of clinicians. Are the results from Study 3 sufficient to assess device safety and effectiveness given (i) possible differences between the demographics and baseline characteristics of the study and the intended U.S. patient population, and (ii) the possible differences in device use across physicians?

I think, in summary, the demographics were not a big issue because it's more reflux and not necessarily the patient population, or the demographics of the patient population were important in that we needed more information broken down in terms of age, gender, degree of reflux. The data was not sufficient to document the effectiveness based on those demographics such as age, grade of reflux and the retreatment. The differences among physicians on device usage was not adequately assessed. The learning curve for different physicians theoretically should be short in that population of physicians that deal with patients with reflux, but it was not necessarily addressed but, by the same token, there were not enough sites or physicians involved.

I won't read the third one but, basically, the post-treatment of grading of reflux not being performed by a blinded evaluator, was that bias important, and, in summary, the bias of reading the studies was not as much an issue as the pre versus post treatment assessment based on either a single radiologist or stratification of the pretreatment analysis versus post treatment was much more important.

No. 4, overall, there was a favorable

risk/benefit ratio but, again, a lack of long-term information made it difficult to completely assess the risk/benefit ratio.

The next question was related to postapproval study and, again, at that point, we decided what was necessary if it was approved, what was necessary if it was not approved. If it was approved, more premarket information was necessary and definitely postmarket surveillance was necessary versus postmarket study in a multicenter with multiple investigators to assess long-term safety and effectiveness. If it was just surveillance, how would we do the surveillance. And, again, we mentioned VCUGs at certain intervals, continuing antibiotics and doing surveillance urine cultures at a set interval or with symptoms and ultrasounds to follow the patients. If the material was not approved, what needs to be done in order to make it more approvable. And the other factor was the 3 potential studies postmarket to assess the percentage of patients who have pyelo and whether or not they had any treatment for their reflux either open or implantable device.

The next one was training for physicians and what was necessary, and I think basically mandatory training was not necessary, but voluntary

training, whether it be via video or hands-on training should be made an option.

The next one was the Directions for Use, was it adequate, and I think that we said from a wholesale standpoint that both the device instructions and the patient needed to be completely revised, with specific inclusion and exclusion criteria, and that that probably needed to be done at a separate FDA meeting.

DR. ANTHONY KALLOO: Okay. Before entertaining a motion recommending an action on this PMA, Dr. Cooper will remind the panel of our responsibilities in reviewing today's premarket approval application and of the voting options open to us.

DR. COOPER: Before you vote on a recommendation, please remember that each PMA has to stand on its own merits. Your recommendation must be supported by the data in the application, or by publicly available information. You may not consider information from other PMAs in reaching a decision on this PMA.

What I'm going to do is go over just some slides to remind the Panel of some definitions. You do have copies of these in the back of all the slides.

(Slide)

The first one is Safety, as defined in the Medical Device Amendments, as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions of intended use outweigh any probable risk.

(Slide)

Effectiveness is defined as reasonable assurance that in a significant portion of the population, the use of the device for its intended uses and conditions of use, when labeled, will provide clinically significant results.

(Slide)

Valid Scientific Evidence consists of well controlled investigations, partially controlled studies, studies and objective trials without matched controls, well documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device.

(Slide)

Your recommendation options for the vote are as follows: Approval, approvable with conditions, or not approvable.

(Slide)

For approval, there are no conditions

attached.

(Slide)

For approvable with conditions, you may recommend that the PMA be found approvable subject to specified conditions such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff. Prior to voting, all of the conditions are discussed by the Panel and listed by the Panel Chair.

(Slide)

Not approvable: If you recommend that the application is not approvable, we ask that you identify the measures that you think are necessary for the PMA to be placed in an approvable form. The reasons for recommending not approvable would be unsafety, the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling. Not approval based on effectiveness: There is reasonable assurances not been given the device is effective under the conditions of use in the labeling. Not approvable on the labeling, based on a fair evaluation of all the material facts and your discussions, you believe the proposed labeling to be false or misleading.

(Slide)

The flow chart is the voting pathway that we follow.

DR. ANTHONY KALLOO: Thank you. I would like to thank Dr. Naida Kalloo for being the primary reviewer of this device The recommendation of the Panel may be approvable, approvable with conditions that are to be met by the applicant, or denial of approval.

Naida, you've already summarized the Panel discussion. Will you make a motion? Whatever motion you make will be discussed. It has to be seconded and then discussed.

DR. NAIDA KALLOO: I would say approvable with significant conditions.

DR. STEINBACH: I'll second that.

DR. ANTHONY KALLOO: This is now open for discussion. I would like to start with Dr. Donatucci to make any comments before we vote.

DR. COOPER: The next step would be to amend the motion with the conditions, one at a time, and vote on each condition.

DR. DONATUCCI: So my discussion is whether I agree with the motion?

DR. STEINBACH: I think next is a specific

condition, right?

DR. COOPER: Correct.

DR. STEINBACH: As a specific condition, I think that the directions for use be changed to include specific contraindications -- for example, Hutch diverticulum.

DR. ANTHONY KALLOO: Would you therefor like to discuss if there are conditions or no conditions to your motion?

DR. NAIDA KALLOO: I would like to get everyone's input about their conditions.

DR. ANTHONY KALLOO: Let's name the conditions, and we'll start with Dr. Donatucci.

DR. DONATUCCI: At this point, I don't have any conditions to add to this motion.

DR. KAEFER: Specific conditions which you've already mentioned as we talked about them here? No. Conditions to the Directions for Use -- and I apologize -- as I looked through this, I didn't have specifically those indications that we talked about for question No. 7, but I've looked at them and I agree. I think that, No. 1, there would have to be very specific contraindications listed without ambiguity, very specific alternatives to treatment without ambiguity, and accurate data based on factual

things we have here as to what the expected outcome is, as far as we know it so far.

Is that what we're looking for? I'm the new guy here.

DR. DiLORETO: The issue is, I think, there's a motion on the table for conditional approval, and we're talking about conditions. The issue is should we -- I mean, only from having been here for a while -- should we decide specifically, just generically speaking, that we vote there should be conditions or not, and move on. We can address specifics to that in a second, but move on to any other issues that we have for this conditional approval, not the specifics of what those conditions would be, because I see three hours of conditions and some other things happening here that we may be spinning our wheels.

DR. GORMAN: As another new kid here, what is the implication of approving with conditions from the regulatory standpoint? Does the device get to market while that data is being collected, or does that device stay off the market while the data is being collected?

DR. SCHULTZ: I'll take a stab at that. The implication depends on what the conditions are.

For instance, if you say we believe this device can be approved pending the following labeling changes, for instance, which is a common set of conditions, then what we would do is, following this meeting, we would go back, review the transcript, listen to what you said both before and hopefully now in terms of defining exactly what you want, and work with the company to come up with a label that we felt met your requirements. So that would be a condition that would be met prior to the device going to market.

If, on the other hand, one of your conditions was we want a postmarket study -- and I tried to outline the different options to you before -- that would be a condition that we and the company would sit down and work out an agreement that a postmarket study would be required and at least a very complete outline of what that study would look like, but the data would not be available to you prior to the device going to market.

I'm trying to think of some other possibilities. Okay. If you said that you would -- that a condition should be that the device could be approved based upon the study that has been done, however, you would like to see a reanalysis performed of some type, or you would like to see some of the

long-term data that's already been collected added to the premarket dataset, those are things again that could be done prior to the device going to market.

So, again, it depends upon exactly what conditions you recommend. Some of them could be met prior to marketing. Obviously, a large postmarket study component would not be met prior to the device going to market.

DR. GORMAN: One more process question. If we approve with conditions, would there be a reconvening of this group or a group like this to analyze that data before allowing marketing access?

DR. SCHULTZ: I'm going to give you another very definite answer -- again, it depends. If you give us clear recommendations and we believe that we can follow those recommendations and get a sense of what it is you want without bringing you all back here to Washington, that's what we will do.

If, on the other hand, you say specifically you can recommend to us that you want to see the data, or you want to see the new labeling, we would take that recommendation to heart. I'm not saying we would definitely follow it, but we would take it to heart.

The other option that we do have -- and

Dr. DiLoreto pointed this out before -- is that rather than reconvening the entire Panel, what we could do is get together with a group of individuals who were most involved in this particular submission and show them the labeling, the outline of the postmarket study, the additional data that was brought in, whatever seemed appropriate, and get their opinion as a sense that the Panel issues had been resolved.

So, again, we have a lot of options.

DR. ANTHONY KALLOO: What I think we have right now is we have a motion that it's approvable with conditions, and that's seconded. So what I would like the Panel to do is to vote on whether -- that either they support this motion that the PMA be approved with conditions, so if I could see a show of hands of the Panelists who support this motion that the PMA is approved with conditions. Please raise your hand.

DR. NAIDA KALLOO: May I make a comment before we do that?

DR. DiLORETO: Call the question.

DR. ANTHONY KALLOO: You've made the motion and there's a second, so I should see at least two hands. So, please vote.

DR. STEINBACH: Not necessarily.

DR. ANTHONY KALLOO: Not necessarily. Okay. Please vote if you agree that the PMA should be approved with conditions. Please raise your hand.

(Show of hands.)

DR. KAEFER: Can I vote on approval with conditions if I can see the data again before it goes to market?

DR. ANTHONY KALLOO: That's a condition, so, yes.

DR. KAEFER: Could I make one comment, maybe make a recommendation that somewhere in between what Dr. DiLoreto's concern were and perhaps where we are right now, and that is that the Panel may want to say -- for instance, you have a motion for approvable with conditions. State in general terms what those conditions are. No. 1, I've heard, revised labeling. Okay. I think that that seems to be an overriding concern. No. 2 -- and I don't in any way mean to put words in your mouth -- but one of the things that I've heard as a possibility is additional long-term data or additional analysis. And No. 3, whether or not you think a postmarket study should be mandated. And maybe if you have those as part of your overall motion, that would be something that people could say, yes, this is something agree with in concept. And

then if you approve that motion, then you can go back and sort of put some meat on those bones, would be my recommendation.

DR. ANTHONY KALLOO: Okay. So we're back to where we were with the conditions, discussing the condition s to make this approvable with conditions, which is what we started to do.

DR. NAIDA KALLOO: Is it all right if I make a comment? The reason that I hesitated before making that judgment is because I think enough information has been presented and I don't think anybody wants to totally wipe out the information that we have and have everybody start from scratch.

I think there's enough information that shows that there's a good safety profile, but the efficacy is the big problem that we need more information. And rather than starting this whole process again, maybe getting much more information and reconvening rather than starting all over again was what my thought process was.

DR. ANTHONY KALLOO: Well, what we are going to do is we are going to follow your advice and we will discuss the conditions of approvability. So I think one condition that we had mentioned -- and you have a list of all the conditions -- if we could just

discuss them and then vote on the conditions.

DR. DiLORETO: Mr. Chairman, can I suggest that the thing that Dan Schultz very adroitly discussed three issues, three general condition issues -- general condition issues -- that could be built into an amendment or however you would like to handle this, into Dr. Kalloo's original motion, and that in general terms we vote yes or no. The specifics can be addressed given the vote. We can go down here and look at lots of nuances in all three of those, or more, categories for specific conditions, but we need to call the question.

DR. ANTHONY KALLOO: So we have two options. One, discuss the conditions and then vote on each condition and then vote whether this approvable or not, or, two, we vote on whether we would like this approved with conditions to be discussed. As the Chair, I'm going to vote for the later.

So, what we are going to vote on right now is whether -- there's been a motion that this be approved with conditions, and I'm going to ask again by a show of your hands, how many of you are in favor of this motion to be approved with conditions. Please raise your hand.

(Show of hands.)

DR. ANTHONY KALLOO: How many vote against this motion being approvable with conditions?

(Show of hands.)

So I have the deciding vote, and my vote is that it is approvable with conditions.

Next we will then discuss the conditions.

DR. NAIDA KALLOO: If the conditions are not met, does it come to another vote?

DR. ANTHONY KALLOO: If we cannot agree on the conditions, it will come to another vote.

DR. STEINBACH: I move that the first condition we should vote on is that the labeling e changed to include specific contraindications and other changes as previously recommended in the discussion.

DR. ANTHONY KALLOO: Any comments to this proposal about the labeling?

DR. NAIDA KALLOO: Again, as was stated before, specific inclusion criteria, specific exclusion criteria -- in other words, specifically excluding Hutch diverticula, duplicated system, high grade reflux, grade V reflux, current dysfunctional voiders, potentially neurogenic bladder --

DR. KAEFER: Nonfunctioning kidney.

DR. NAIDA KALLOO: -- nonfunctioning

kidney, inclusion criteria, say, specifically grades II-IV with specific informed consent to the parents stating that the success rate may be low for the higher grades of reflux and they may subsequently need additional procedures, even surgery; the need for antibiotics to continue until there's proof that the reflux is gone; the comparison with respect to age, gender, specifically with the different grades of reflux, and comparisons with spontaneous rates of resolution, and even the risk of urinary tract infections with the manipulations that are required.

DR. ANTHONY KALLOO: Can we now approve a vote on this particular amendment to the labeling? Those in favor of the amendments that were made, please raise your hand.

(Show of hands.)

Those against these amendments, please raise your hand.

(Show of hands.)

So the amendment has been passed, as stated.

DR. NAIDA KALLOO: Now, specifically the patient brochure as a separate one from the devices, changing the patient brochure.

DR. ANTHONY KALLOO: Actually, I'd like to

do postmarketing study.

DR. STEINBACH: I move that a condition for approval that a postmarketing study be conducted at several sites that has sufficient numbers of patients to establish efficacy in age subsets and gender subsets.

DR. ANTHONY KALLOO: Is there a second to that motion?

DR. KAEFER: Yes, I second it.

DR. ANTHONY KALLOO: Can we discuss any further amendments to that postmarketing study which is a multicentered study that was recommended?

DR. NEWMAN: Can we say that it has to be done in the U.S.?

DR. ANTHONY KALLOO: Yes, we could say that it has to be done in the U.S. Any other amendments or comments on the postmarketing study in terms of what you would like to see on that?

(No response.)

Okay. Dr. Kalloo, would you summarize the Panel's recommendations for a postmarketing study?

DR. NAIDA KALLOO: The postmarketing study would need to be done in the United States with multicenters, multiple physicians. The efficacy would need to be addressed and stratified in terms of age,

gender, grade of reflux, and any other demographics such as race, number of treatments, and be much more specific, and I think that the specifics probably need to be addressed in a different agenda, or separate agenda.

DR. ANTHONY KALLOO: Do you have an addition to that?

DR. STEINBACH: The definition of effectiveness be defined as 0 reflux.

DR. SCHULTZ: Could I ask a question? Would you want to comment on controls or lack of controls?

DR. DiLORETO: I think there's enough data -- the controls are the nontreated group, and there's thousands of medicated prophylactically kids with reflux and enough data in the literature that in this case historic data to me would be acceptable because it's everywhere.

DR. STEINBACH: And because the third study shows that there was a difference between the placebo group, so it did verify the historical record.

DR. KAEFER: But it verified it with extremely small numbers. I don't agree completely with that last statement. As long as it's age, gender, stratified, dysfunctional voiding, et cetera,

then we do have plenty of historical numbers to do that, but one has to be very specific with how we actually match these patients up.

DR. ANTHONY KALLOO: Can the Panel vote on this particular amendment. Those in favor of the amendment, please raise your hands, as described by Dr. Kalloo. Those in favor, please raise your hands.

(Show of hands.)

Those that are against this amendment, please raise your hands.

(No response.)

Other amendments to the other -- conditions -- I'm sorry.

DR. NEWMAN: You want more data on the present site, right?

DR. NAIDA KALLOO: More long-term data on the patients in studies 1, 2 and 3.

DR. ANTHONY KALLOO: In terms of data, in terms of long-term efficacy and complications.

DR. NAIDA KALLOO: Number of episodes of urinary tract infections, whether these urinary tract infections were investigated with a VCUG, at what point, ultrasound results long-term, and things like that. Again, it's kind of hard to give a comprehensive specific list of everything that we

need, but we certainly do need much more data.

DR. ANTHONY KALLOO: Should the data be from both Study 3 and Study 1 populations? Is there where we should be asking them to provide that data from?

DR. DiLORETO: I think there's two issues. The issue is data with respect to reflux ending at a year, or whether there's going to be recurrent infections beyond a year. They've obviously got data going back to '95 that --

DR. ANTHONY KALLOO: That's Study 1.

DR. DiLORETO: I understand -- that may be difficult to extrapolate, but I think that we need to see that data and come up with some statistical analysis of that to say that what we're doing is correct here.

The other issue is there are potential migration issues or local tissue effect issues -- and, again, there's a cohort of patients going back five years now that could be looked at, and this could actually be part of a subset of postmarketing surveillance patients that are already being followed. But we need more numbers -- and I hate to be negative, and by no token is this a slam on the company, but I'm personally very disappointed that we're approving

something like this based on 31 patients. Ten years of sitting here has sort of trained me to do things, and I'm very disappointed. Notwithstanding that this is probably an excellent product and probably will work very well, but we're doing this based on 31 patients. And, again, it's not personal, it's not an issue with any of the Panel members or the sponsor. I have a problem with this.

DR. ANTHONY KALLOO: Your points are noted. Yes?

DR. GORMAN: I would not like that data collection to be limited to the patients in Studies 1, 2 and 3. These two institutions that have presented data today obviously have many patients, and I would like to know their failure rate. I would like to know in their institutions if these people are easy to identify, what number get reimplanted surgically, what number develop pyelonephritis, what number have other surgical procedures after Deflux, and I don't think it should be limited to the 210 patients they presented the data on, but should be expanded to easily identifiable patients that received this treatment at their institutions.

DR. DiLORETO: Again, the onus is on the company. This is a condition. These are things that

we are requiring before the product is released, and it is of paramount importance, and the only analogy I can make is from years ago, a similar Panel approved a gastric exclusion product that ended up being a disaster. And not that that would happen here but, again, we don't have enough numbers. And so whether it's done in committee, whether it's done with us over the phone or faxes or whatever, that subset of patients needs to be looked at. In my heart, I believe this is safe. In my heart, I believe this is an excellent treatment modality. I think it far surpasses anything that we've seen to-date, including the Teflon and the other panels I've sat on, but there isn't enough data.

DR. ANTHONY KALLOO: Well, I think that's what the committee is doing right now, we're providing the stipulations and we're saying exactly how it should be done, the way it should be done in the U.S., with multicentered studies, with multiple investigators.

So, I think the Panel has a sense of what you're saying in terms that this is probably a good product, but we are now requiring the FDA to fulfill our requirements of having a multicentered U.S. study, which will do exactly what you ask for.

DR. KAEFER: But before actually doing that, we have 1500 patients from Dr. Capozza, and if this technique really is straightforward to use and with reasonably reproducible results, we potentially now have 3, 4, 5 people with a number of patients, and if there's not a big standard deviation in their success rates, there may be more towards the answer of is this really good data or is it spurious? But we need that before even this postmarket thing, in my opinion.

DR. ANTHONY KALLOO: Well, we could say that we would like before a multicenter prospective trial to have that data. If the data looks good, then we should proceed with a multicenter prospective trial. If the data looks bad --

DR. NAIDA KALLOO: Or if there is not enough data with the patients that they already have in a comprehensive manner, then we need more patients. I certainly echo everybody's comments. I feel a little uncomfortable with more data saying that, but I also think that we all agree that -- it's been used in Europe for a long time and, overall, the patients seem to do well. We just need some more of that information available to us and, if we don't get it, then we don't get it and we say no.

DR. ANTHONY KALLOO: So, therefore, Dr. Kalloo, can you summarize this as a recommendation -- I'm sorry, I didn't see.

DR. GORMAN: Maybe it's my somewhat rigid upbringing in the past, but we are basically asking the company to do a premarketing pivotal efficacy study. I don't want to put too much of a fine point on that, but that's what we're asking for.

DR. KAEFER: Which they may have already done, and we just need to see that data. They can actually get it to us.

DR. ANTHONY KALLOO: Do you want to make a comment on that point?

DR. SCHULTZ: I was going to make a comment before that, but just so I understand exactly what I'm hearing. I think -- and please feel free to correct me if I'm wrong. What I'm hearing is that there's a sense of the committee that there is a positive risk/benefit, and that this device will probably do good things for kids in the U.S., but there's a concern about both the amount and the length of the data that's been presented to the Panel thus far.

I'm hearing very clearly that you would like to have additional studies done postmarketing and

following more patients in the United States, in an uncontrolled but prospective study at multiple sites, to be able to establish some of the different stratifications and some additional data that has not been presented to you so far.

I'm also hearing that in the premarket period there's a sense of the committee that additional data exists with the investigators in Europe that could be collected and could provide us with a sort of better picture of the device performance that would give us the "reasonable assurance" of safety and effectiveness that we need to have the product go to market.

And my recommendation, I guess, to you would be -- if that is, in fact, your sense -- is to let us work with the company and see if we can get that data, put that data in a format and, again, perhaps work with a subcommittee of this committee to make sure that it meets your needs. And then move on, at the same time negotiate the labeling based on that data and the format of the postmarket study. That's what I'm hearing.

DR. ANTHONY KALLOO: I believe that to be accurate, and I could ask Dr. Kalloo to repeat all of that so that we can vote on that, but maybe if we can

just agree -- if you agree with this statement, to raise your right hand, and if you disagree, then we will see. So, if you are in favor of that, please raise your right hand.

(Show of hands.)

DR. STEINBACH: I think it has a clarification. There's two issues. One is we are asking for a postmarket multicentered study, and separate from that we are also additionally asking for the data from the current two studies -- apparently, the second is not legally obtainable -- to verify long-term effectiveness of this. So, maybe to speed up the discussion, should we put the approval based on long-term efficacy as a separate condition?

DR. ANTHONY KALLOO: So you're saying we should divide it into two parts?

DR. STEINBACH: I think we've already passed the first part of it. Now the second part is a further addition condition to approval would be that the produce in two of the first three studies should be effective after two years.

DR. DONATUCCI: I'd just like to make a comment here. I've been sitting quietly for most of this discussion, but I am the second senior most member at the table today.

DR. SCHULTZ: You have a plaque.

DR. DONATUCCI: That's right, I have a plaque. We've already voted and we've discussed the conditions fairly extensively in the presence of everyone here, including the FDA, and of course we are an advisory panel and the FDA will take our advice under consideration. I'm not sure how much more specific recommendations you require from us at this point.

DR. ANTHONY KALLOO: Well, you can look at the algorithm. Every amendment that's been made has to voted upon.

DR. DONATUCCI: Fine, I think we should continue to vote, but we -- I would remember only that we are advising and not necessarily designing a new trial in the space of a very short period of time.

DR. ANTHONY KALLOO: Any other comments before we vote?

DR. GORMAN: Yes, one. I think that we've talked some about postmarketing surveillance, and I also think that it was not clear -- at least it was not clear to me -- that I would also like there to be some premarketing conditions looking at the long-term data from the patients that may be available from these institutions.

DR. ANTHONY KALLOO: So maybe we should vote on the premarketing conditions about long-term data. Those in favor of a condition of approval that the premarketing long-term data meets the satisfaction of the FDA, please raise your hand.

(Show of hands.)

Those against?

(No response.)

Okay. It's unanimous.

Then the second vote should be on a postmarketing study which is a prospective multicentered trial with multiple investigators, with the parameters that were discussed. If you are in favor of this, please raise your hand.

(Show of hands.)

Those against.

(No response.)

Again, this is a unanimous decision.

Other conditions that we should -- any suggestions about other conditions for the approvability of this study, please could you mention it now and we'll discuss it now. Anything anyone else wants to add?

DR. DiLORETO: The only comment being that some of the premarket data, once it's analyzed -- and

this is only a comment -- be used specifically to go back into -- assuming it's what we need and we agree and it's there -- that that data, when it's analyzed, be used and stratified to go back into the labeling of the product. And, again, I'm not going to make any specific comments because I don't know what that data is going to show, but hopefully in committee, FDA committee -- and we'll share it with some of us -- that that be looked at and taken and built into the labeling requirements of the product.

DR. NAIDA KALLOO: That sounds to me basically we need to inform both the doctors and the patients based on the data that's available. It needs to be specific based on the data available, not the 3-5 year, 80-percent success rate that's in there that's not supported by the data that we have.

DR. DiLORETO: Correct, and there may be a whole lot more data than is on the table today that we can make a better judgment on where we're going with this. It's just my only negativism is just, again, the data that was put in front of us today.

DR. ANTHONY KALLOO: I think that's it. I'd like to thank all the --

DR. STEINBACH: Dr. Kalloo, we have to vote whether everyone agrees that it's approvable with

the conditions that have been approved.

DR. ANTHONY KALLOO: That's correct. We have one more vote. That is to vote on if everyone agrees with the conditions that have been approved, please raise your hands.

(Show of hands.)

Those against, please raise your hands.

(Show of hands.)

So the motion that the PMA is approved with the conditions that have been stipulated has been passed.

I would like to thank the Panelists --

DR. SCHULTZ: One more comment? Let me just make sure that I'm clear. We've got conditional approval with three conditions, correct?

DR. ANTHONY KALLOO: Three conditions.

DR. SCHULTZ: One is labeling, two is additional data --

DR. NAIDA KALLOO: Premarketing.

DR. SCHULTZ: -- premarket based on the studies that have already been done, with proper analysis and incorporation of that data into the labeling, and three is a U.S. multisite postmarket study, correct? Is that what I'm hearing?

DR. ANTHONY KALLOO: Correct.

DR. SCHULTZ: Then I would agree that a final vote needs to be taken based on those -- approvable with those three conditions, and what we need to do is go around and poll each member of the Panel as to their vote and their reasons for voting the way they did.

DR. ANTHONY KALLOO: Then we will start off with -- we've already voted, the vote was 4 to 2. So I'll ask each member of the Panel to comment on his or her vote and the reasons for voting the way they did, starting with Dr. Kalloo.

DR. NAIDA KALLOO: As I stated before, I think that the safety issue is probably okay. I think that the alternative to what we have available is probably okay. I'm just uncomfortable with the information that we have available and approving it outright, and I would like some more information. And that's why I voted approved with conditions.

DR. DONATUCCI: My vote reflects my sense of the PMA as presented to us today as being insufficient for approval, and the concept of basically doing a multicentered trial postmarket I don't know -- in my opinion, might not be feasible. And that's the reason for my no vote.

DR. KAEFER: My vote is for approval with

conditions. I believe this device, based on the information we have, has favorable risk/benefit profile, but as we heard from the statistician and as everyone here around the table has echoed, the numbers are just too small. And if we take away any thought about how good this product might be, we just don't have statistical proof that's good enough in order to show that it really is what we think it might be. And so we need that premarket data before we even think of going on to that next step, and I think that's what the amendments are.

DR. KAEFER: I voted for approval. I think the effectiveness shown in small numbers is -- makes it probable that this is a good device. I think that allowing the multicentered, multiphycian as a postmarket is in the interest of public safety.

DR. STEINBACH: I voted approval.

DR. DiLORETO: In spite of my negativism, I am voting for approval with conditions, however, I would implore upon the FDA and the committee of the FDA that the premarketing issue still needs to be addressed. Again, it appears to be safe. The effectiveness albeit isn't 80 percent, but there is an effectiveness built into this. It needs to be stratified so the users and the receivers and their

parents understand the ramifications of this versus other modalities. Long-term issues, again, will be looked at. Again, some of their -- and I'll call it postmarketing data because they have that data available, and through some internal -- through the numbers that will built into the U.S. postmarketing data, I, again -- and I'll echo Dr. Donatucci even though we're voting differently -- the numbers were not there, and -- not specifically to these sponsors, but to any other sponsors -- this data shouldn't be coming to the FDA with 31 patients, particularly children -- shouldn't be presented. This is not an orphan drug. This is not -- this has huge ramifications based on the potential number of children that could, again, be exposed to this or be benefitted from it -- it goes both ways -- but 31 patients -- and I just want everyone to remember that.

DR. GORMAN: I'd like to echo everything my colleague said except I voted in the other direction. Valid scientific evidence was the criteria to which it was supposed to be held. I did not think valid scientific evidence was presented for efficacy for this product. And I share my colleagues' concern that premarketing and postmarketing collection of data may not be sufficient to resolve those issues that I

have.

DR. SCHULTZ: I think that while the Consumer Reps don't get to vote, my understanding is that they do get to comment. So you have an opportunity to voice your opinion even absent a vote, if you would like. You are not forced.

DR. NAIDA KALLOO: I'd like to make one other comment as being on the other side and being that surgeon and having that little life in your hands and making sure that you go from start to finish, and you follow the family, and you deal with them, and each urinary tract infection with that high fever and you want to do something to help them. It's still hard for a family to go through a major urologic surgery. I love it, but it's still hard for a family to go through it. And if this provides an alternative for that, then I think that we should probably consider that when we know we have an opportunity to do it, but I agree with everybody that we have to have the numbers. We have to make sure that it's safe. But I also, as a physician and a parent, want to make sure that my kid doesn't have to go through a big, long surgical procedure with potential complications, if they don't necessarily have to and if there is another alternative.

DR. STEINBACH: I would like to respectfully disagree with Dr. DiLoreto. I think we've had supplemental information for 210 patients. And we don't have a placebo control for 210 patients, but we do have evidence of effectiveness.

DR. NEWMAN: I do have a comment. Even though I'm not a physician, it just strikes me that what bothers me, I didn't realize, as being on FDA that we are taking European data. I've seen a lot of procedures in this world where we can extrapolate that in the U.S., and it's not done. And that somewhat disturbs me that we're just looking at European data. And that's why I really push the postmarket study, although I agree with you, I'm not sure that's feasible.

DR. ANTHONY KALLOO: I want to thank the Panel -- that's the fourth time -- but I want to thank the Panelists. This concludes the report of recommendations of the Panel on the P000029 Q-Med AB on Reflux Injectable Gel. On behalf of the FDA, I'd like to thank the entire panel. This meeting is adjourned.

(Whereupon, at 3:30 p.m., the meeting was adjourned.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Medical Devices Advisory Committee

Before: DHHS/PHS/FDA/CDRH

Date: October 19, 2000

Place: Rockville, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.